Sotatercept for the Treatment of Pulmonary Arterial Hypertension: PULSAR Open-label Extension

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Supplemental material

Treatment emergent adverse events of special interest (AESI)

In prior sotatercept clinical oncology studies in chemotherapy-induced anemia and osteolytic bone disease in multiple myeloma, leukopenia, neutropenia (including febrile neutropenia), granulocytopenia, and thrombocytopenia have been described as TEAEs. Per health authority request, leukopenia, neutropenia, and thrombocytopenia were identified as AESIs in this study.

Standard multiple imputation

Missing at Random (MAR) assumption was made to perform standard Multiple Imputation (MI). For missing points, monotonous regression was used to fill in the missing points in the order of time points using values calculated at the previous time points. The analysis involved the following steps:

1. The missing data were filled in m times to generate m complete data sets using monotonous regression model accounting for baseline value, randomization stratification factor, and if necessary, additional covariates such as age and other secondary endpoints at different visits in the imputation model.

2. The m complete data sets were analyzed by using standard procedures. ANCOVA with the randomization stratification factor and baseline value as the covariate and Mixed effect Model Repeat Measure (MMRM) model as mentioned above were used for analysis here.

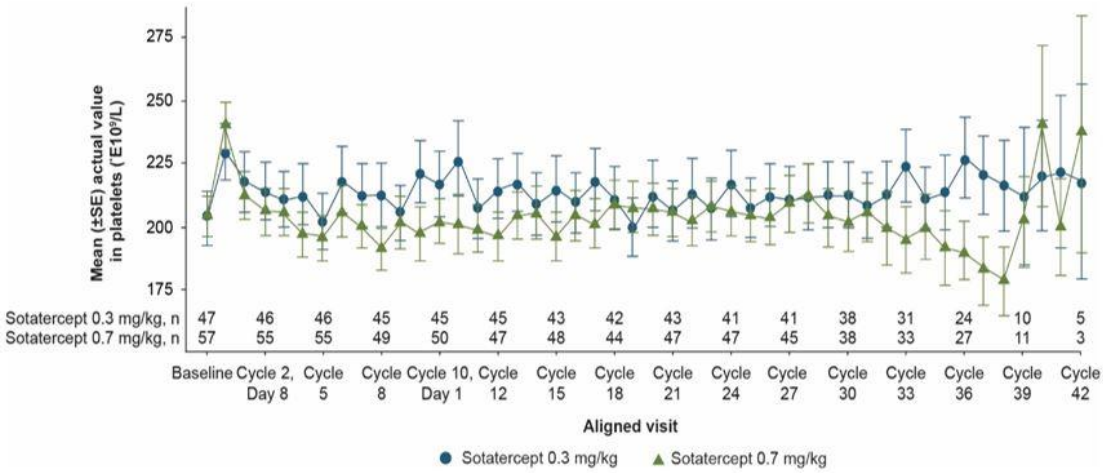
3. The results from the m complete data sets were combined for the inference.

Changes to concomitant PAH medications during the open-label extension period

During the extension period, concomitant PAH medications were adjusted for six participants. Three participants receiving triple background PAH therapy with an endothelin receptor antagonist (ERA), phosphodiesterase 5 inhibitor (PDE5i), and prostacyclin was switched from either intravenous (IV) (one participant) or subcutaneous (SC) (two participants) to an oral prostacyclin. One participant receiving triple background PAH therapy with an ERA, PDE5i, and prostacyclin was switched from inhaled to oral prostacyclin. One participant receiving triple background therapy with an ERA, PDE5i, and oral prostacyclin had their ERA switched to a soluble guanylate cyclase (sGC). Lastly, one participant required escalation of PAH therapy from monotherapy with a PDE5i to dual therapy with a PDE5i and addition of an ERA.

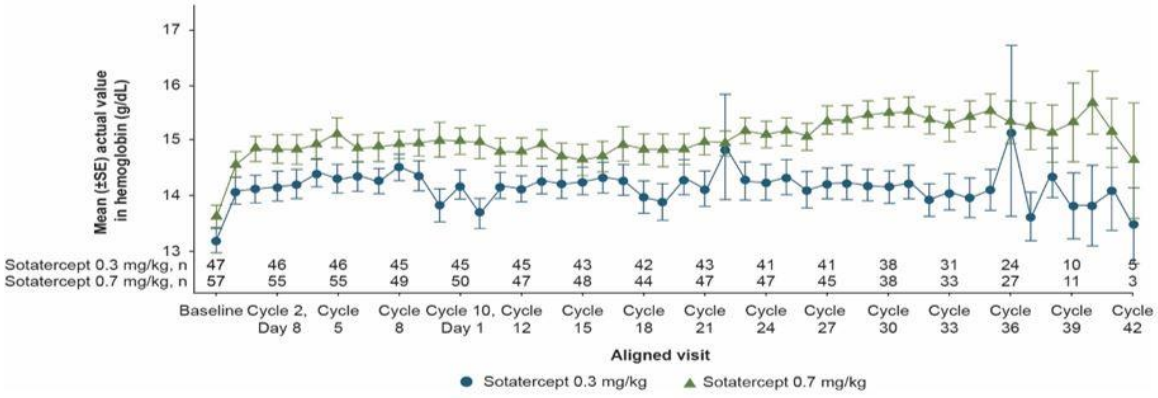
Supplementary figures

Figure S1. Change in platelet count by visit in all sotatercept-treated participants



Aligned baseline is the latest pre-dose assessment obtained on or before Cycle 1 Day 1 for the continued sotatercept treatment group and is the assessment obtained on Cycle 9 Day 1 for the placebo-crossed treatment group. Only visits with at least two participants in both treatment groups are shown.

Figure S2. Change in hemoglobin levels by visit in all sotatercept-treated participants



Aligned baseline is the latest pre-dose assessment obtained on or before Cycle 1 Day 1 for the continued sotatercept treatment group and is the assessment obtained on Cycle 9 Day 1 for the placebo-crossed treatment group. A cycle refers to a treatment cycle, which is 21 days (±3 days). Only visits with at least two participants in both treatment groups are shown.

Figure S3. Change from baseline to end of placebo-controlled treatment period and from baseline to Months 18–24 in pulmonary vascular resistance

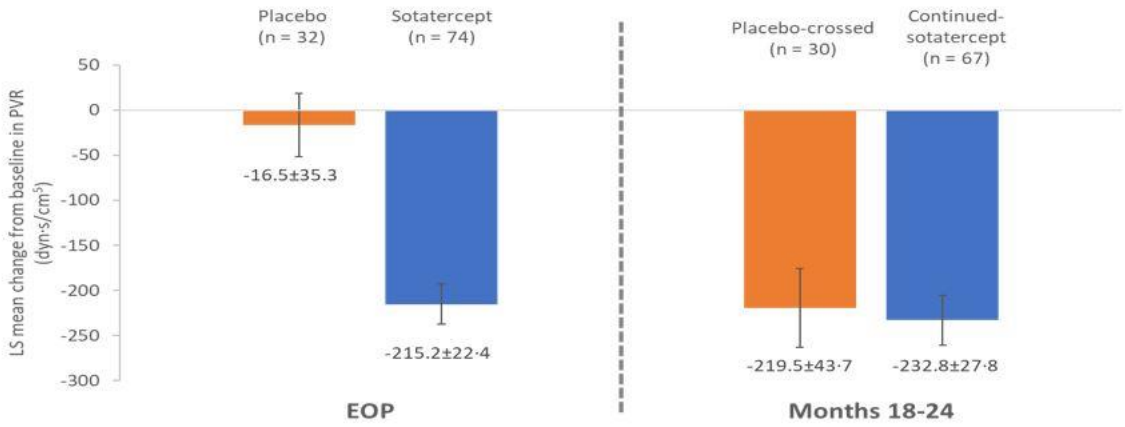


Figure shows LS mean change from baseline to Months 18–24 in PVR in each group. LS mean difference at EOP between placebo and sotatercept group: –198·9 (95% CI, −281·5 to −116·3) dyn·s/cm^5; P < 0·0001. LS mean difference at Months 18–24 between placebo-crossed and continued-sotatercept group: −13·3 (95% CI, −113·2 to 86·7) dyn·s/cm^5; P = 0·7945. Data are from FAS for Placebo-controlled Period and FAS-E for Extension Period and using standard multiple imputation. Groups were compared using ANCOVA with baseline WHO FC and baseline PVR as covariates. Error bars represent SE. ANCOVA = analysis of covariance; CI = confidence interval; EOP = end of placebo-controlled treatment period; FAS-E = extension period full analysis set; LS = least-squares; PVR = pulmonary vascular resistance; SE = standard error; WHO FC = World Health Organization functional class.

Figure S4. Change from baseline to end of placebo-controlled treatment period and from baseline to Months 18–24 in six-minute walk distance

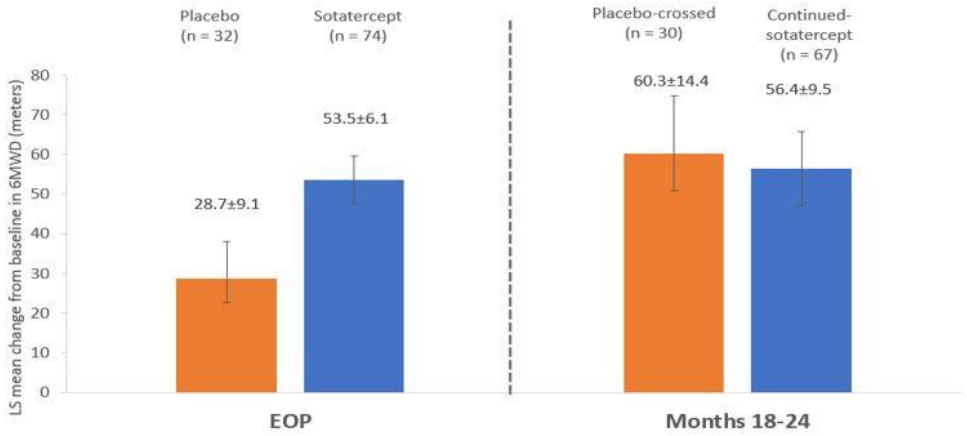


Figure shows LS mean change from baseline (Month 0) to Months 18–24 in 6MWD in each group. LS mean difference at EOP between placebo and sotatercept group: 24·9 (95% CI, 3·1 to 46·6) dyn·s/cm^5; P < 0·025. LS mean difference at Months 18–24 between placebo-crossed and continued sotatercept group: −3·9 (95% CI, −37·6, 29·7) m; P = 0·8194. Data are from FAS for Placebo-controlled Period and FAS-E for Extension Period and using standard multiple imputation. Groups were compared using ANCOVA with baseline WHO functional class and baseline 6MWD as covariates. 6MWD = six-minute walk distance; ANCOVA = analysis of covariance; CI = confidence interval; EOP = end of placebo-controlled treatment period; FAS-E= extension period full analysis set; LS = least-squares; NTproBNP = N-terminal pro-B-type natriuretic peptide; PVR = pulmonary vascular resistance; WHO FC = World Health Organization functional class.

Figure S5. Change from baseline to end of placebo-controlled treatment period and Months 18–24 in N-terminal pro-B-type natriuretic peptide

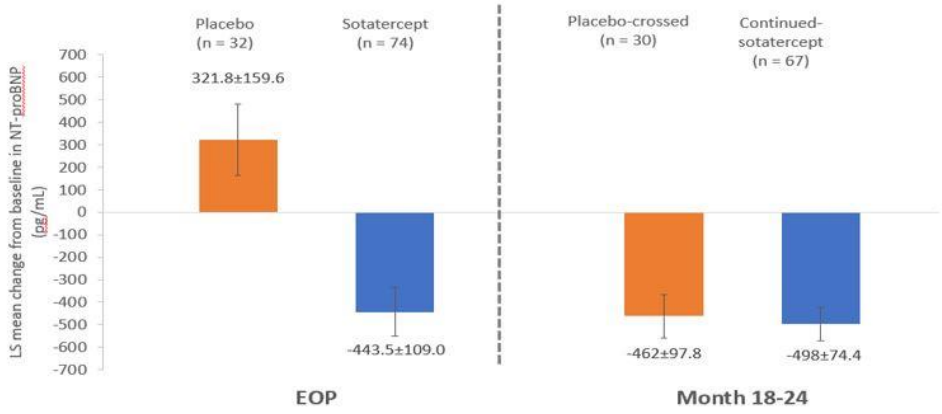


Figure shows LS mean change from baseline (Month 0) to Months 18–24 in NT-proBNP in each group. LS mean difference at EOP between placebo and sotatercept group: −764·6 (95% CI, −1142·79 to −386·42) pg/mL; P < 0·0001. LS mean difference at Months 18−24 between placebo-crossed and continuedsotatercept group: −36·0 (95% CI, −274·74, 202·73) pg/mL; P = 0·7675. Data are from FAS for Placebo-controlled Period and FAS-E for Extension Period and using standard multiple imputation. Groups were compared using ANCOVA with baseline WHO functional class and baseline result as covariates. Error bars represent SE. 6MWD = six-minute walk distance; ANCOVA = analysis of covariance; FAS-E = extension period full analysis set; LS = least-squares; NT-proBNP = N-terminal pro-B-type natriuretic peptide; WHO FC = World Health Organization functional class.

Figure S6. Change from baseline to end of placebo-controlled treatment period and from baseline to Months 18–24 in World Health Organization functional class

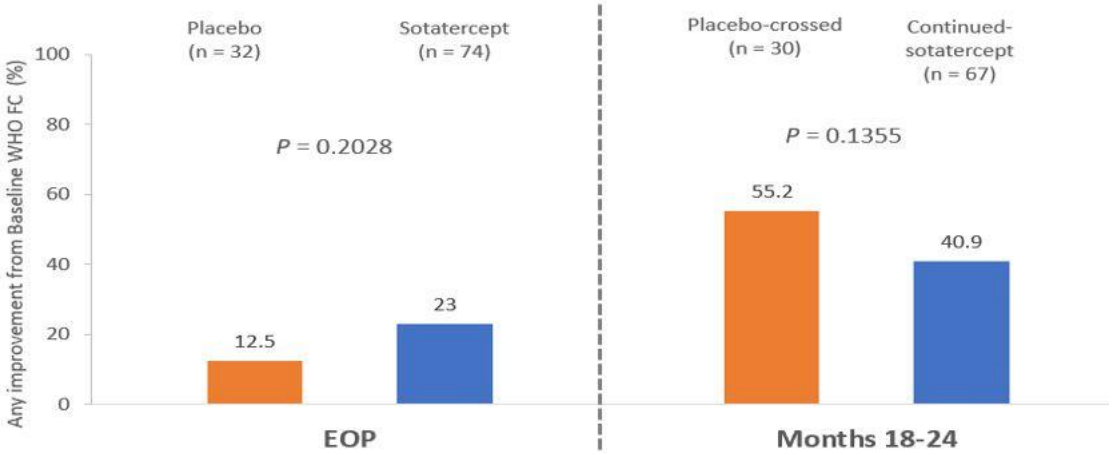


Figure shows the percentage of participants with any improvement in WHO functional class from baseline to Months 18−24. Data are from FAS for Placebo-controlled Period and FAS-E for Extension Period. Comparison between groups using CMH method stratified by baseline WHO FC. 6MWD = 6-minute walk distance; CMH = Cochran-Mantel-Haenszel; EOP = end of placebo-controlled treatment period; FAS-E = extension period full analysis set; NT-proBNP = N-terminal pro-B-type natriuretic peptide; WHO FC = World Health Organization functional class.

Table S1. Baseline demographics and clinical characteristics

	Placebo-crossed (n = 30)	Continued-sotatercept (n = 67)	Total (N = 97)
Age, years			
Mean (SD)	45.3 (13.6)	48.6 (14.4)	47.6 (14.2)
Median	46.0	48.0	47.0
Min, max	21, 71	19, 80	19, 80
Female, n (%)	24 (80.0)	62 (92.5)	86 (88.7)
Race, n (%)			
White	28 (93.3)	61 (91.0)	89 (91.8)
Black or African American	0 (0.0)	4 (6.0)	4 (4.1)
Other	2 (6.7)	2 (3.0)	4 (4.1)
Length of time since PAH diagnosis, years			
Mean (SD)	7.3 (5.3)	8.0 (5.8)	7.8 (5.6)
Median	6.8	7.4	7.4
Min, max	0.3, 21.9	0.7, 26.2	0.3, 26.2
WHO Group 1: PAH, n (%)			
Drug or toxin-induced PAH	0 (0.0)	6 (9.0)	6 (6.2)
Heritable PAH	6 (20)	10 (14.9)	16 (16.5)
Idiopathic PAH	18 (60)	36 (53.7)	54 (55.7)
PAH-associated with CTD	4 (13.3)	14 (20.9)	18 (18.6)
PAH associated with simple, congenital systemic-to-pulmonary shunts ≥1 year following repair	2 (6.7)	1 (1.5)	3 (3.1)
Background PAH therapy, n (%)			
Monotherapy	2 (6.7)	5 (7.5)	7 (7.2)
Double therapy	12 (40.0)	23 (34.3)	35 (36.1)
Triple therapy	16 (53.3)	39 (58.2)	55 (56.7)
Prostacyclin infusion therapy, n (%)			
Yes	9 (30.0)	26 (38.8)	35 (36.1)

Data are from the FAS-E.

CTD = connective tissue disease; FAS-E = Extension period full analysis set; PAH = pulmonary arterial hypertension; SD = standard deviation; WHO = World Health Organization.

Table S2. Most common (≥10%) treatment-emergent adverse events in all sotatercept-treated participants

Preferred term, n (%)	Placebo to sotatercept 0.3 mg/kg (n = 15)	Placebo to sotatercept 0.7 mg/kg (n = 15)	Continuing sotatercept 0.3 mg/kg (n = 32)	Continuing sotatercept 0.7 mg/kg (n = 42)	Combined sotatercept 0.3 mg/kg (n = 47)	Combined sotatercept 0.7 mg/kg (n = 57)	Total (N = 104)
Headache	4 (26.7)	7 (46.7)	12 (37.5)	11 (26.2)	16 (34.0)	18 (31.6)	34 (32.7)
Diarrhoea	3 (20.0)	4 (26.7)	13 (40.6)	9 (21.4)	16 (34.0)	13 (22.8)	29 (27.9)
Oedema peripheral	4 (26.7)	5 (33.3)	11 (34.4)	8 (19.0)	15 (31.9)	13 (22.8)	28 (26.9)
Nasopharyngitis	4 (26.7)	6 (40.0)	10 (31.3)	5 (11.9)	14 (29.8)	11 (19.3)	25 (24.0)
Nausea	2 (13.3)	4 (26.7)	8 (25.0)	8 (19.0)	10 (21.3)	12 (21.1)	22 (21.2)
Dizziness	4 (26.7)	1 (6.7)	8 (25.0)	8 (19.0)	12 (25.5)	9 (15.8)	21 (20.2)
Fatigue	3 (20.0)	3 (20.0)	8 (25.0)	7 (16.7)	11 (23.4)	10 (17.5)	21 (20.2)
Arthralgia	2 (13.3)	5 (33.3)	7 (21.9)	5 (11.9)	9 (19.1)	10 (17.5)	19 (18.3)
Epistaxis	2 (13.3)	3 (20.0)	8 (25.0)	6 (14.3)	10 (21.3)	9 (15.8)	19 (18.3)
Pain in extremity	2 (13.3)	3 (20.0)	7 (21.9)	6 (14.3)	9 (19.1)	9 (15.8)	18 (17.3)
Upper respiratory tract infection	3 (20.0)	1 (6.7)	6 (18.8)	7 (16.7)	9 (19.1)	8 (14.0)	17 (16.3)
Back pain	1 (6.7)	3 (20.0)	8 (25.0)	3 (7.1)	9 (19.1)	6 (10.5)	15 (14.4)
Haemoglobin increased	1 (6.7)	5 (33.3)	1 (3.1)	8 (19.0)	2 (4.3)	13 (22.8)	15 (14.4)
Myalgia	1 (6.7)	3 (20.0)	5 (15.6)	6 (14.3)	6 (12.8)	9 (15.8)	15 (14.4)
Urinary tract infection	2 (13.3)	0 (0.0)	7 (21.9)	6 (14.3)	9 (19.1)	6 (10.5)	15 (14.4)
Hypokalaemia	3 (20.0)	0 (0.0)	5 (15.6)	6 (14.3)	8 (17.0)	6 (10.5)	14 (13.5)
Vomiting	1 (6.7)	2 (13.3)	6 (18.8)	5 (11.9)	7 (14.9)	7 (12.3)	14 (13.5)
Gastroenteritis	2 (13.3)	0 (0.0)	6 (18.8)	5 (11.9)	8 (17.0)	5 (8.8)	13 (12.5)
Thrombocytopaenia	3 (20.0)	1 (6.7)	3 (9.4)	6 (14.3)	6 (12.8)	7 (12.3)	13 (12.5)
Iron deficiency	3 (20.)	1 (6.7)	2 (6.3)	6 (14.3)	5 (10.6)	7 (12.3)	12 (11.5)
Pyrexia	1 (6.7)	1 (6.7)	4 (12.5)	6 (14.3)	5 (10.6)	7 (12.3)	12 (11.5)
Telangiectasia	2 (13.3)	3 (20.0)	3 (9.4)	3 (7.1)	5 (10.6)	6 (10.5)	11 (10.6)

Safety population (includes all randomized participants who received at least one dose of study treatment). A TEAE has a start date on or after the first dose of treatment and up to 8 weeks after the last dose of treatment. TEAEs were coded using MedDRA Version 23.1.

TEAE = treatment-emergent adverse event.

Table S3. Most common (≥10%) treatment-emergent adverse events in all participants by time-period

	All sotatercept-treated† (Months 1–6)						
Preferred term, n (%)	Placebo to sotatercept 0.3 mg/kg (n = 15)	Placebo to sotatercept 0.7 mg/kg (n = 15)	Continuing sotatercept 0.3 mg/kg (n = 32)	Continuing sotatercept 0.7 mg/kg (n = 42)	Combined sotatercept 0.3 mg/kg (n = 47)	Combined sotatercept 0.7 mg/kg (n = 57)	Total (N = 104)
Headache	1 (6.7)	3 (20.0)	8 (25.0)	6 (14.3)	9 (19.1)	9 (15.8)	18 (17.3)
Diarrhoea	1 (6.7)	2 (13.3)	7 (21.9)	6 (14.3)	8 (17.0)	8 (14.0)	16 (15.4)
Nasopharyngitis	4 (26.7)	4 (26.7)	3 (9.4)	4 (9.5)	7 (14.9)	8 (14.0)	15 (14.4)
Peripheral oedema	1 (6.7)	2 (13.3)	4 (12.5)	5 (11.9)	5 (10.6)	7 (12.3)	12 (11.5)
Nausea	1 (6.7)	2 (13.3)	3 (9.4)	5 (11.9)	4 (8.5)	7 (12.3)	11 (10.6)
Hypokalaemia	2 (13.3)	0 (0.0)	4 (12.5)	5 (11.9)	6 (12.8)	5 (8.8)	11 (10.6)
Epistaxis	1 (6.7)	1 (6.7)	4 (12.5)	5 (11.9)	5 (10.6)	6 (10.5)	11 (10.6)
	All sotatercept-treated† (Months 7–12)						
	(n = 15)	(n = 15)	(n = 31)	(n = 37)	(n = 46)	(n = 52)	(n = 98)
Headache	4 (26.7)	3 (20.0)	4 (12.9)	1 (2.7)	8 (17.4)	4 (7.7)	12 (12.2)
Diarrhoea	1 (6.7)	2 (13.3)	6 (19.4)	1 (2.7)	7 (15.2)	3 (5.8)	10 (10.2)
Nasopharyngitis	0 (0.0)	3 (20.0)	6 (19.4)	1 (2.7)	6 (13.0)	4 (7.7)	10 (10.2)
	All sotatercept-treated† (Months 13–18)						
	(n = 14)	(n = 15)	(n = 30)	(n = 35)	(n = 44)	(n = 50)	(n = 94)
	No data to report						
	All sotatercept-treated† (Months 19–24)						
	(n = 12)	(n = 14)	(n = 30)	(n = 35)	(n = 42)	(n = 49)	(n = 91)
	No data to report						

*Safety population during the placebo-controlled period; †A TEAE has a start date on or after the first dose of treatment and up to 8 weeks after the last dose of treatment.

A TEAE has a start date on or after the first dose of treatment and up to 8 weeks after the last dose of treatment. TEAEs were coded using MedDRA Version 23.1.

n = number of participants with TEAEs; TEAE = treatment-emergent adverse event.

Table S4. Treatment-emergent adverse events by time-at-risk exposure-adjusted incidence rate in all sotatercept-treated participants

TEAE	Placebo to sotatercept 0.3 mg/kg (n = 15)	Placebo to sotatercept 0.7 mg/kg (n = 15)	Continuing sotatercept 0.3 mg/kg (n = 32)	Continuing sotatercept 0.7 mg/kg (n = 42)	Combined sotatercept 0.3 mg/kg (n = 47)	Combined sotatercept 0.7 mg/kg (n = 57)	Total (N = 104)
Any, n (%) TAR-EAIR/100 PYAR (95% CI)	13 (86.7) 257.5 (149.5, 443.5)	15 (100.0) 830.1 (500.4, 1,376.9)	32 (100.0) 584.1 (413.1, 826.0)	42 (100.0) 473.3 (349.8, 640.5)	45 (95.7) 427.5 (319.2, 572.5)	57 (100.0) 533.7 (411.7, 691.9)	102 (98.1) 481.0 (396.1, 584.0)
Related to treatment, n (%) TAR-EAIR/100 PYAR (95% CI)	10 (66.7) 78.0 (42.0, 145.0)	13 (86.7) 154.9 (89.9, 266.7)	20 (62.5) 62.4 (40.3, 96.8)	29 (69.0) 84.5 (58.7, 121.5)	30 (63.8) 66.9 (46.8, 95.7)	42 (73.7) 98.3 (72.6, 133.0)	72 (69.2) 82.2 (65.2, 103.6)
AESI†, n (%) TAR-EAIR/100 PYAR (95% CI)	5 (33.3) 25.7 (10.7, 61.8)	1 (6.7) 4.0 (0.6, 28.4)	5 (15.6) 8.3 (3.4, 19.8)	7 (16.7) 10.0 (4.8, 21.0)	10 (21.3) 12.5 (6.7, 23.2)	8 (14.0) 8.4 (4.2, 16.8)	18 (17.3) 10.3 (6.5, 16.3)
Serious, n (%) TAR-EAIR/100 PYAR (95% CI)	5 (33.3) 25.7 (10.7, 61.8)	3 (20.0) 13.3 (4.3, 41.3)	8 (25.0) 14.1 (7.1, 28.2)	16 (38.1) 24.8 (15.2, 40.4)	13 (27.7) 17.1 (9.9, 29.4)	19 (33.3) 21.8 (13.9, 34.2)	32 (30.8) 19.6 (13.9, 27.7)
Serious related to treatment, n (%) TAR-EAIR/100 PYAR (95% CI)	2 (13.3) 8.4 (2.1, 33.8)	0 (0.0)	1 (3.1) 1.5 (0.2, 10.6)	2 (4.8) 2.7 (0.7, 10.6)	3 (6.4) 3.3 (1.1, 10.3)	2 (3.5) 2.0 (0.5, 7.9)	5 (4.8) 2.6 (1.1, 6.3)
Leading to treatment discontinuation, n (%) TAR-EAIR/100 PYAR (95% CI)	1 (6.7) 4.0 (0.6, 28.3)	0 (0.0)	2 (6.3) 3.0 (0.8, 12.0)	7 (16.7) 9.1 (4.4, 19.2)	3 (6.4) 3.3 (1.1, 10.1)	7 (12.3) 6.9 (3.3, 14.4)	10 (9.6) 5.2 (2.8, 9.6)
Leading to study discontinuation, n (%) TAR-EAIR/100 PYAR (95% CI)	1 (6.7) 4.0 (0.6, 28.3)	0 (0.0)	2 (6.3) 3.0 (0.8, 12.0)	7 (16.7) 9.1 (4.4, 19.2)	3 (6.4) 3.3 (1.1, 10.1)	7 (12.3) 6.9 (3.3, 14.4)	10 (9.6) 5.2 (2.8, 9.6)
Leading to death, n (%) TAR-EAIR/100 PYAR (95% CI)	1 (6.7) 4.0 (0.6, 28.3)	0 (0.0)	0 (0.0)	2 (4.8) 2.6 (0.6, 10.3)	1 (2.1) 1.1 (0.2, 7.7)	2 (3.5) 1.9 (0.5, 7.8)	3 (2.9) 1.5 (0.5, 4.8)

TEAEs in all sotatercept-treated participants.

TAR-EAIR is presented in number of participants with events per 100 total person-years at risk, which was calculated as (number of participants with events/total person-years at risk)*100 for each treatment arm.

For participants with events, PYAR was calculated as sum of (start date of the first event − first sotatercept treatment date + 1)/365.25. For participants with no events, PYAR was calculated as sum of (follow-up date − first sotatercept treatment date + 1)/365.25.

†Defined as any TEAE of leukopaenia, neutropaenia, or thrombocytopaenia.
AESI = adverse event of special interest; CI = confidence interval; n = number of participants with TEAEs; PYAR = total person-years at risk; TEAE = treatment-emergent adverse event; TAR-EAIR = time-at-risk exposure-adjusted incidence rate.

Table S5. Dose modifications – all sotatercept treated participants

	Placebo to sotatercept 0.3 mg/kg (n = 15)	Placebo to sotatercept 0.7 mg/kg (n = 15)	Continuing sotatercept 0.3 mg/kg (n = 32)	Continuing sotatercept 0.7 mg/kg (n = 42)	Combined sotatercept 0.3 mg/kg (n = 47)	Combined sotatercept 0.7 mg/kg (n = 57)	Total (N = 104)
Number of dose reductions, n (%)							
0	9 (60.0)	9 (60.0)	22 (68.8)	23 (54.8)	31 (66.0)	32 (56.1)	63 (60.6)
1	3 (20.0)	4 (26.7)	8 (25.0)	12 (28.6)	11 (23.4)	16 (28.1)	27 (26.0)
2	3 (20.0)	2 (13.3)	2 (6.3)	7 (16.7)	5 (10.6)	9 (15.8)	14 (13.5)
Reasons for dose reduction							
TEAE or treatment-emergent AEs of special interest, n (%)	5 (33.3)	1 (6.7)	6 (18.8)	8 (19.0)	11 (23.4)	9 (15.8)	20 (19.2)
Haemoglobin ≥ 18 g/dL, n (%)	1 (6.7)	5 (33.3)	0 (0.0)	6 (14.3)	1 (2.1)	11 (19.3)	12 (11.5)
Unresolved elevated haemoglobin, n (%)	0 (0.0)	2 (13.3)	4 (12.5)	2 (4.8)	4 (8.5)	4 (7.0)	8 (7.7)
Haemoglobin increase, n (%)	0 (0.0)	1 (6.7)	0 (0.0)	4 (9.5)	0 (0.0)	5 (8.8)	5 (4.8)
Increase after previous reduction, n (%)	5 (33.3)	3 (20.0)	6 (18.8)	8 (19.0)	11 (23.4)	11 (19.3)	22 (21.2)
Increase from 0.3 to 0.7 mg/kg, n (%)	6 (40.0)	1 (6.7)	18 (56.3)	7 (16.7)	24 (51.1)	8 (14.0)	32 (30.8)

Data displayed are from the first dose of sotatercept. Participants with multiple reductions or delays or increase may have more than one reason presented.

n = number of participants with TEAEs; TEAE = treatment-emergent adverse event.

Table S6. Change from baseline to end of placebo-controlled treatment period and Months 18–24 in haematocrit-adjusted pulmonary vascular resistance

Haematocrit-adjusted PVR, dynes*sec/cm^5	Placebo-crossed (n = 30)	Continued-sotatercept (n = 67)	Total (N = 97)
Baseline	838.8 (288.2) n = 29	863.3 (405.4) n = 67	855.9 (372.6) n = 96
EOP	811.1 (357.5) n = 29	572.1 (278.1) n = 67	644.3 (321.8) n = 96
Change from baseline to EOP	−27.7 (266.5) n = 29	−291.2 (243.0) n = 67	−211.6 (277.1) n = 96
Months 18–24	572.0 (294.1) n = 24	532.6 (218.2) n = 57	544.3 (241.9) n = 81
Change from baseline to Months 18–24	−297.8 (236.0) n = 24*	−301.6 (258.1) n = 57*	−300.5 (250.3) n = 81

All values are mean (SD). Data are from the FAS-E. Baseline = Month 0 (start of the study).

**P*-values < 0.0001

EOP = end of placebo-controlled treatment period; FAS-E = extension period full analysis set; PVR = pulmonary vascular resistance; SD = standard deviation.

Table S7. Change from baseline to Month 18–24 by delayed-start analysis

	Placebo-crossed (n =30) LS Mean (SE)	Continued-sotatercept (n = 67) LS Mean (SE)	LS mean difference (SE) [multiple imputation]	*P* value
PVR, dyn·s/cm^5	−219.5 (43.7)	−232.8 (27.8)	−13.3 (51.0)	0.7945
6MWD, meters	60.3 (14.4)	56.4 (9.5)	−3.9 (17.2)	0.8194
WHO FC*	16/29 (55.2)	27/66 (40.9)	N/A	0.1355
NT-proBNP, pg/mL	−462.0 (97.8)	−498.0 (74.4)	−36.0 (121.8)	0.7675

*Values presented are proportion of participants with any improvement from baseline WHO class (%); participants affected by COVID-19 were taken out of the denominator and missing are treated as non-responders.

6MWD = six-minute walk distance; LS = least-squares; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PVR = pulmonary vascular resistance; SE = standard error; WHO FC = World Health Organization functional class.

Table S8. Change from baseline to aligned Month 6 in 6MWD and WHO FC by dose

	Sotatercept 0.3mg/kg (n = 47) LS Mean (SE)	Sotatercept 0.7mg/kg (n = 57) LS Mean (SE)	LS mean difference (SE) [multiple imputation]	*P* value
6MWD, meters	41.0 (16.5)	36.0 (17.4)	−5.0 (9.9)	0.6172
WHO FC	−0.3 (0.6)	−0.2 (0.6)	0.1 (0.1)	0.5874

Aligned baseline is standard baseline for participants originally randomized to sotatercept 0.3 or 0.7mg/kg and Month 6 for patients originally randomized to placebo. The aligned month 6 is Month 6 for participants originally randomized to sotatercept 0.3 or 0.7mg/kg and Month 12 for participants originally randomized to placebo.

6MWD = six-minute walk distance; LS = least-squares; SE = standard error; WHO FC = World Health Organization functional class.